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Hydroxypropyl-β-cyclodextrin (HPBCD) in Insoluble Drug-Loaded Nanoparticles Dissolution Studying: A New Approach to Overcoming Sink Limitations

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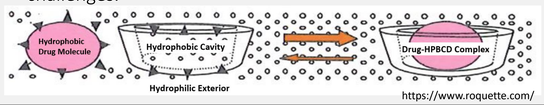
INTRODUCTION

- The increasing prevalence of BCS Class II compounds in drug discovery, which often face dissolution challenges, increases the need for better test methods.
- Maintaining sink conditions for discriminating dissolution characterization, particularly for low solubility drugs is more challenging.
- The use of hydroxypropyl-β-cyclodextrin (HPBCD) in the dissolution buffer is one possible way to address these challenges.



PROPOSE(S)

Three model drugs with different solubilities were employed. Their saturation concentrations in three common dissolution medias and HPBCD solution were compared.

The release behavior of model drugs, incorporated into nanoparticles, was assessed with and without the presence of HPBCD.

Figure out whether HPBCD in the dissolution buffer can help maintain sink conditions for BCS Class II compounds, without interfering with drug release.

METHOD(S)

- Three BCS Class II drugs with different solubility, Cholecalciferol (VD3, MW 384.6, LogP7.5), Lovastatin (LVT, MW:404.5, LogP:4.5), and Indomethacin (IND, MW:357.8, LogP:3.4) were used as model drugs.
- Saturation drug concentrations were measured via UPLC after 3 days shaking at 37℃. Recovery tests mixed solutions with blank NPs, analyzed post-shaking.
- Stability studies involved exposing solutions to 37℃ for 48 hours.
- Nanoparticles loaded with VD3, LVT, and IND were prepared via oil-in-water emulsion method, tested in 37℃ media. UPLC measured cumulative drug release; SPSS Statistics (v26) analyzed release patterns.

RESULT(S)

1. Hydrophobicity drugs (e.g.,VD3) prefer to remain in the hydrophobic cavity of HPBCD (Figure 1A) and form solubilization complexes. Figure 1B,E, and F show VD3 no longer exists in crystalline form, but forms a complex with HPBCD

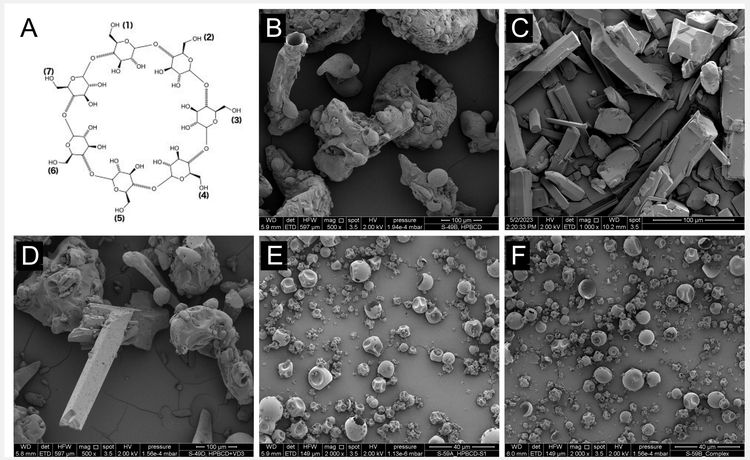


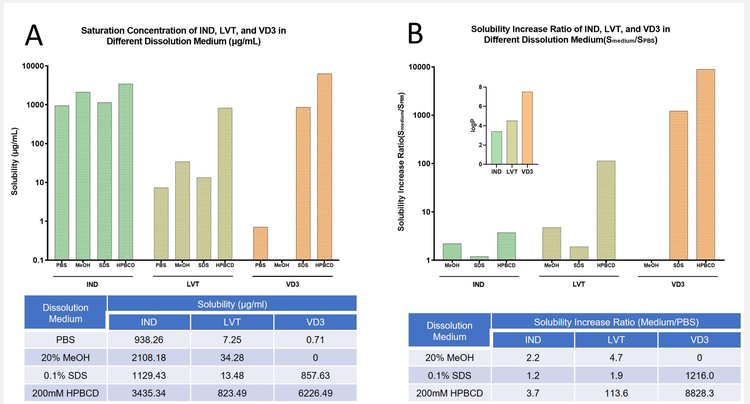
Figure. 1: (A) 2D structure of HPBCD; (B) HPBCD; (C) cholecalciferol (VD3), (D) physical mixture of VD3 and HPBCD; (E) spray dried HPBCD; (F) spray dried cholecalciferol–HPBCD complex particles.

3. Three model drugs are stable in HPBCD buffer. The presence of blank nanoparticles (NPs) did not interfere with the measurement of the drugs.

	Indomethacin			Lovastatin		VD3		
Starting Concentration (μg/ml)	256.24	25.06	2.83	95.19	9.70	240.24	23.68	2.95
Recovery Rate from NPs Suspension (% of Starting Concentration)	100.11	98.48	98.11	101.05	98.30	98.57	99.89	93.87
37°C 48 hr Stability (% of Starting Concentration)	105.61	95.92	95.18	98.70	95.44	98.37	99.65	100.54

Figure 3. IND, LVT and VD3 recovery rate from NPs suspension and stability in HPBCD solution

2. Compared with the other three commonly used dissolution buffers, HPBCD can help the drug to obtain the best solubility. (Figure 2A) HPBCD also has the best effect in increasing solubility ratios (S_{buffer}/S_{PBS}). (Figure B)



Dissolution Medium	Solubility (μg/ml)		
	IND	LVT	VD3
PBS	938.26	7.25	0.71
20% MeOH	2108.18	34.28	0
0.1% SDS	1129.43	13.48	857.63
200mM HPBCD	3435.34	823.49	6226.49

Dissolution Medium	Solubility Increase Ratio (Medium/PBS)		
	IND	LVT	VD3
20% MeOH	2.2	4.7	0
0.1% SDS	1.2	1.9	1216.0
200mM HPBCD	3.7	113.6	8828.3

Figure 2. Solubility change of hydrophobic drugs in different dissolution mediums (A) Saturated concentration of IND, LVT, and VD3 in different dissolution mediums (μg/ml); (B) Solubility increase ratio of IND, LVT, and VD3 in different dissolution medium to PBS

4. HPBCD can encapsule the drug into its hydrophobic cavity that helps to maintain sink conditions for throughout drug release process and the release model has not been changed.

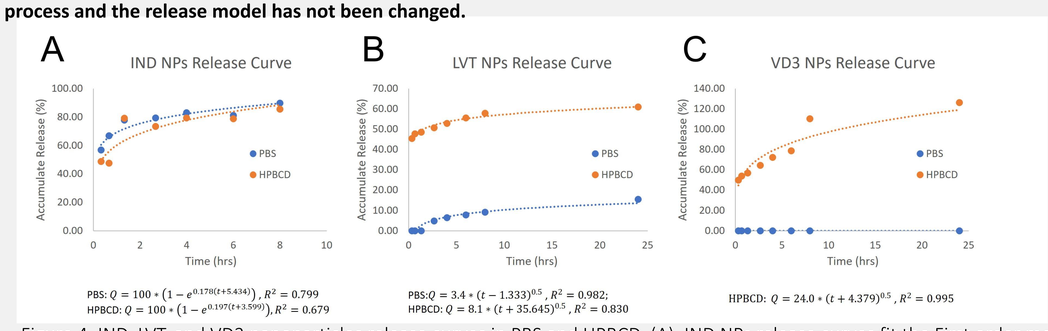


Figure 4. IND, LVT, and VD3 nanoparticles release curves in PBS and HPBCD. (A). IND NPs release curves fit the First order model both in PBS and HPBCD. (B) LVT NPs release curves fit the Higuchi model both in PBS and HPBCD (C) VD3 nanoparticles in HPBCD release curves fit the Higuchi model

CONCLUSION(S)

HPBCD could enhance the solubility of hydrophobic drugs significantly. This phenomenon is proportional to the drugs' LogP value. In dissolution medium HPBCD play a solubilizing role. The drug release mechanism is not interfered with while the sink condition was maintained.

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